Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Assessing the effect of blood type on death and a novel scoring system to assess clinical course in patients with COVID-19

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Abstract

Background: Coronavirus disease (COVID-19) continues to lead to worldwide morbidity and mortality. This study examined the association between blood type and clinical outcomes in patients with COVID-19 measured by a calculated morbidity score and mortality rates. The secondary aim was to investigate the relationship between patient characteristics and COVID-19 associated clinical outcomes and mortality.

Methods: Logistic regression was used to determine what factors were associated with death. A total morbidity score was constructed based on overall patient's COVID-19 clinical course. This score was modeled using Quasi-Poisson regression. Bayesian variable selection was used for the logistic regression to obtain a posterior probability that blood type is important in predicting worsened clinical outcomes and death.

Results: Neither blood type nor Rh+ status was a significant moderator of death or morbidity score in regression analyses. Increased age (adjusted Odds Ratio=3.37, 95% CI=2.44–4.67), male gender (aOR=1.35, 95% CI=1.08-1.69), and number of comorbid conditions (aOR=1.28, 95% CI=1.01-1.63) were significantly associated with death. Significant factors in predicting total morbidity score were age (adjusted Multiplicative Effect=1.45; 95% CI=1.349-1.555) and gender (aME=1.17; 95% CI=1.109-1.243). The posterior probability that blood type influenced death was only 10%.

Conclusions: There is strong evidence that blood type was not a significant predictor of clinical course or death in patients hospitalized with COVID-19. Older age and male gender led to worse clinical outcomes and higher rates of death; older age, male gender, and comorbidities predicted a worse clinical course and higher morbidity score. Race was not a significant predictor of death in our population and was associated with an increased, albeit not significant, morbidity score.

Introduction

The first case of coronavirus disease (COVID-19), caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China in December 2019. The respiratory virus was quickly transmitted across the world, being declared a pandemic by the WHO in March 2020. As of July 26th 2021, the virus has spread to over 213 countries and territories, infected over 194 million people, and caused over 4.1 million deaths worldwide.[1] In the United States, over 34 million people have acquired virus with more than 600,000 deaths.[1]

It is imperative to identify patient characteristics that may lead to significant morbidity and mortality; as the identification of vulnerable populations may lead to the implementation of prevention strategies, prognostication tools, and potential treatment options going forward.

Thus far, research has demonstrated that adults 65 years or older and those with comorbid conditions, such as hypertension, chronic kidney disease, obesity, and diabetes, are at increased risk of severe illness from COVID-19.[2] Studies show that patients of Black race contribute to a disproportionately higher rate of infection and mortality from COVID-19.[3-67,8]

Efforts have been made to uncover additional associations between patient characteristics and COVID-19. The relationship between blood type and COVID-19 emerged in March, 2020, demonstrating individuals with blood type A are more susceptible to acquiring infection and subsequent morbidity from the virus; however, other studies have failed to show evidence that an association exists between blood group and mortality among COVID-19 patients.[9-13] Most recently, patients with type A or AB has been associated with an increased risk of mechanical ventilation and disease severity, compared to those with type B or O.[14]

The majority of available data focuses on mortality rates of COVID-19. The effect of patient characteristics on clinical course is lacking in the literature; this is most likely owing to the difficulty of quantifying a patient's clinical course associated with a COVID-19 infection.

The primary aim of this study is to investigate the association between blood type and clinical outcomes, measured quantitatively by a calculated morbidity score and mortality, among patients with confirmed COVID-19 infection. Our secondary objective is to investigate how other patient characteristics (specifically age, gender, pre-existing medical comorbidities, and race) affect clinical outcomes, measured quantitatively by a calculated morbidity score and mortality, among patients with confirmed COVID-19 infection.

Methods

This study was approved by the Institutional Review Board at Louisiana State University Health Sciences Center and the Research Review Committee at University Medical Center of New Orleans. In this retrospective chart review, pre-entered patient data was collected from our system wide electronic medical record (EMR) Epic. We identified all patients over the age of 18 with a confirmed laboratory diagnosis of COVID-19 in the outpatient setting or emergency department (ED) from March 1 2020 to June 18 2020 and had a blood type on file using splicer-dicer function in the EMR and recorded into a password protected, de-identified database. Patient demographics, including age, sex, ethnicity and race were recorded. Ethnicity and race were determined by the patient. Patient body mass index (BMI), blood type, and comorbid conditions were obtained and logged in our database. Additionally, various events during a patient's COVID-19 diagnosis and treatment were documented, including myocardial infarction, stroke, deep vein thrombosis, respiratory compromise necessitating oxygen supplementation, respiratory failure requiring intubation, acute kidney injury (AKI), and AKI requiring hemodialysis or continuous renal replacement therapy. Pharmaceutical treatments and length of hospital stay were also collected from EMR review.

Statistical analysis was performed in R statistical software version 4.0.2. Means and standard deviations of continuous covariates are reported across blood type groups, with categorical covariates reported as the count and percentage of each category within a blood type. Categorical demographic covariates were compared between blood type groups using Fisher exact tests, with continuous variable distributions being compared via a Kruskal Wallace test. Logistic regression was performed to determine what factors predict death in COVID-19 hospitalized patients.

Bayesian variable selection was used in the logistic regression model to obtain a probability on the importance of blood typing in predicting death. We assume a spike-and-slab prior, with a prior probability of inclusion set to .10 to encourage sparsity.[15] The slab distribution was assumed to be flat to encourage the variable selection to be done based on the data relationships entirely. Posterior sampling was done via adaptive Markov Chain Monte Carlo (MCMC) with Metropolis within Gibbs steps using for loops in R statistical software. 20,000 posterior samples were drawn using stochastic search variable selection and the first half of the draws were discarded for burnin.

Since outcomes for COVID-19 patients are complex, we created a total morbidity score based on a variety of potential patient events. Three individuals independently assessed 21 clinical events that may occur during a COVID-19 illness and assigned a score to rate the severity of each event. The range of the scoring system was determined by the individual's preference. Afterwards, the three researchers met, compared different scoring systems, and agreed on a single morbidity score. Each event was rated compared to a base score of "outpatient diagnosis of COVID-19", which was felt to be the least invasive clinical event.

Each event adds points to a patient's total morbidity score, with the highest contributing factor being death. This score takes a complex patient medical history during COVID-19 treatment, and reduces it to a single optimality score – similarly to that used by Hobbs et al.[16] This score differentiates between two patients who died. For example, a patient who spends 3 weeks in the hospital while being intubated but later dies – suffers more and requires greater hospital

resources than a patient who arrives and dies immediately. In this scoring system, treatments like remdesivir, steroids, hydroxychloroquine, and azithromycin increase a patient's overall morbidity score – since these treatments were only given if a patient's condition began to deteriorate. This scoring system is shown in table 2, and was determined through a consensus of the 3 researchers. As an example of the scoring system, consider a patient who was admitted, hospitalized for 3 days, had a stroke, and died. This patient's morbidity score is 2+5+3+50=55. Since these total morbidity scores are whole numbers, we determine factors related to increased or decreased scores using Quasi-Poisson regression models. Quasi-Poisson regression models were used due to the presence of significant overdispersion ($p<.001$) in Poisson regression models. Overdispersion was tested for using the function *dispersiontest* in the *aer* package. Quasi-Poisson regression was performed using the *glm* in R.

Results

There were 670 patients overall who had blood type available and were treated at University Medical Center New Orleans from March 1 2020 to June 18 2020 for COVID 19. One patient was removed because they had a missing BMI value, leaving 669 patients for inference. Prior to adjusting for other potential confounders for blood typing, we examined demographic differences between the four blood typing groups in table 1. Patients with an A blood type were more likely to be male, and patients with AB blood type were less likely to be male. Likewise, patients with blood type B or AB were more likely to be Black. 472 (70.6%) of patients were Black, 5 (.7%) patients were native Americans or Hawaiians, 7 patients were Asian, and 185 patients were white, unknown, or listed as other.

The scoring system used for determining overall COVID-19 related morbidity scores is shown in table 2. Patient scores were calculated by determining whether a patient experienced each row event and adding scores from the appropriate scoring system – based on patient medical histories. Table 3 displays the number of patients and percent who experienced each unique event used to compute the total morbidity score.

The death rate in the A and B blood type groups was about 3% higher than the death rates for types O and AB, but this difference was not statistically significant.

The box plots of the patient scores by blood typing is shown in figure 1 for the scoring system considered. It appears that the AB blood type group has slightly lower total morbidity scores compared to A, B, and O, but this difference was not significant.

Logistic regression was performed to determine whether blood typing affected the probability of death, after adjusting for other possible confounders. The adjusted odds ratios and associated 95% confidence intervals are displayed in figure 2 (top). Confidence intervals that overlap with 1 (as indicated by the horizontal line) show a non-significant relationship between that covariate and death.

Increased age (adjusted odds ratio, aOR = 3.37, 95% CI = 2.44 – 4.67), male gender (aOR = 1.35, 95% CI = 1.08-1.69), and number of comorbid conditions (aOR = 1.28, 95% CI = 1.01-1.63) were the only covariates that were significantly associated with death. P-values for comparing blood types A, B, and AB against O were .78, .41, .97, respectively, reflecting the

confidence interval overlap with 1. The pairwise p-values for testing whether blood types A, B, and AB were equivalent in terms of predicting death were .572 for A vs B, .46 for B vs AB, and .80 for A vs AB. We tested whether blood types or Rh+ status was needed using a general linear hypothesis test based on the deviance and found a p-value of .93, indicating that these covariates could be discarded without a large loss in precision for predicting death.

Additionally, Bayesian variable selection with a prior probability of inclusion of .10 was used to determine which covariates are most important and allows exploration of a wide range of combinations of covariates in predicting death. Figure 2 (bottom) displays the marginal posterior probability of inclusion for each variable, where larger values indicate that covariate is important in predicting death. The marginal probability for blood type was determined by examining whether any of the blood types or Rh+ were important. This probability was .10 giving strong evidence (with probability .90) that blood type is not important in predicting death.

Finally, we wanted to examine how blood types relate to a patient's overall clinical course, excluding death. First, we performed Quasi-Poisson regression to obtain confidence intervals for the multiplicative effect, which are shown in table 4. Intervals that do not contain 1 indicate a significant effect on total morbidity score. For the scoring system, the only significant factors in predicting total morbidity score were age (adjusted multiplicative effect, aME = 1.45, 95% CI=1.349-1.555) and male gender (aME=1.17, 95% CI= 1.109-1.243). Black patients did have a higher comorbidity score, but this difference was not quite significant with a p-value of .059. All p-values corresponding to blood related covariates were above .46 for each scoring system. The

pairwise p-values for testing whether blood types A, B, and AB were equivalent in terms of morbidity score were all greater than .77.

Discussion

Primary outcome: Blood Type

In this single institutional, retrospective analysis, we found persistent evidence that there is no association between blood type and clinical course or mortality rates.

Since the advent of COVID-19, there have been mixed results reported with regards to the link between blood type and death rates among those infected. Some studies have reported an association between blood type and morbidity while others have not.[9,10,12,13] The literature supports that infection rates and mortality may be influenced by blood type in various disease states; however, our data, in conjunction with other research groups, indicates that this is not the case in COVID-19 infections.[13,17,18]

Our study is unique in the way in which clinical course was measured. By assigning a grade to each adverse clinical event, we were able to produce a morbidity score that quantifies the clinical experience of a patient during their COVID-19 infection. Our study is the first to attempt to assign a morbidity score in COVID-19. It was our intent that this morbidity score would better characterize the clinical course of our patients and aid in a more precise depiction of their experience. By illuminating the association between blood type and clinical course, blood type may have served as a morbidity forecaster. However, blood type did not predict a worse clinical score and thus should not be used in the prognostication of clinical course in patients infected with SARS-CoV-2.

In our study, the majority of patients had O type blood (49%), followed by A (27%), B (19%), and AB (5%). In the United States, roughly 44% have O type blood, 42% with A blood type, 10% with B type, and only 4% with AB type.[19] Our population appears to underrepresent A blood type while overrepresenting B blood type. The majority of our patients were Black and our Black patients were more likely to have type B or AB blood, which may account for the increase in B type blood represented in this study.

It is worthy to note that the finding that mortality in the A and B blood type groups was roughly 3% higher than the death rates for types O and AB with the difference not reaching statistical significance. Males were more likely to have A blood type, whereas women were more likely to be AB type. We found that males were associated with higher morbidity and mortality scores than females after adjusting for blood type; therefore, this finding is most likely due to other factors (as discussed below).

As we have found that blood type does not predict outcomes of patients infected with COVID-19, we call for future studies to focus on other hematological components that may impact clinical course and death rates in this infection. Elucidating the role that various hematological factors play in the morbidity and mortality associated with COVID-19 may have both prognostic and therapeutic indications.

Secondary outcomes: Age, Gender, Comorbidities, Race

Not surprisingly, age was found to be a significant predictor of both morbidity score and mortality. This is consistent throughout the literature and likely owing to what has been referred

to as the "twilight of immunity".[20-25] In a recent review, Nikolich-Zurgich and colleagues provides an overview of age-related changes associated with the adaptive immune system and lymphoid organs which leaves the elderly particularly susceptible to infectious organisms. [25] Specifically, age-related changes in monocytes and B cells exist, both having more activation with age, leading to more pro-inflammatory cytokines.[26] Current research has demonstrated that critically ill patients produce more pro-inflammatory cytokines compared to those who experience mild or moderate COVID-19 related illness.[27]. [27] As such, elderly individuals may be more prone to cytokine storms leading to worse morbidity and mortality.

Our findings demonstrated that male patients were more likely to have significantly worse outcomes than female patients. In fact, all states except Massachusetts have reported than more men have died from COVID-19 infections than women. [28] The disproportionate death rate among men is most likely multifactorial and the result of biopsychosocial factors.[29] From a biological perspective, the X chromosome carries genetic information for immune-related function. [29] As such, women tend to have more robust innate and adaptive immune responses when compared to their male counterparts. Immune response is also modulated by steroid hormones. With women having more estrogen and progesterone than men, this may account for gender specific outcomes.[30] As previously discussed, inflammatory cytokines increase with age but also disproportionately in males more than females.[26]Lastly, men are reported to have more systemic ACE2 receptors, the receptor by which COVID-19 virus gains cellular access in the pulmonary, renal, gastrointestinal, central nervous system, and cardiovascular system. [31-33] With regards to psychological and social factors, men were more likely than women to downplay the seriousness of COVID-19 and participate in large social gatherings.[34,35] Men were also less

likely to engage in adequate handwashing, consistently wear a mask, and seek medical care when needed. [29,35-38]

A common theme that has been reported throughout this pandemic is that the presence of comorbidities confers a worse clinical course and greater risk of COVID-19 related mortality.[39-44] Patients with a history of hypertension, diabetes, and chronic kidney disease had worse clinical outcomes and increased mortality.[40,41,45-50] In a large federal electronic medical chart review of 31,461 patients, it was found that those with myocardial infarction, congestive heart failure, dementia, chronic pulmonary disease, liver disease, renal and metastatic solid tumor were also at risk of morbidity and mortality associated with COVID-19. [51] The reason for this may be due to the increased systemic inflammation that occurs in the chronic disease state.[39]

Lastly, our study found that Black patients have significantly more comorbidities than non-Black patients, but morbidity score and rate of mortality among Black patients was not significantly different than other races. The majority of the patients assessed were Black, comprising 70.5% of our study population. Our hospital's patient population consists of 43.7% Black persons who are served both outpatient and inpatient. It is unclear why Black patients were disproportionately contracting COVID-19. The racial differences in COVID-19 related morbidity and mortality that has been reported in the literature is multifactorial, consisting of workplace setting and opportunities to work from home. Reports state that Black people are significantly less likely to have occupations that allow for remote work, which may be an example of structural racism that deserves a deeper investigation beyond the score of this paper.[52] Other studies have found that

when SES is accounted for, the differences in morbidity do not exist. [8] Our hospital is a safety net hospital that cares for the indigent population; our patients are relatively homogenous with respect to SES and economic backgrounds. Our study indicates that, when compared to other patients of similar social and economic backgrounds, Black people are being diagnosed with COVID-19 more than other races. This finding is intriguing and we call for future work to investigate why Black patients were disproportionately affected by COVID-19, when SES was relatively homogenous within our patient population.

Limitations

This study was a retrospective investigation; therefore, there is potential for selection bias. Given that our primary aim was to investigate the impact of blood type on clinical course and mortality rates, having blood type on file was an inclusion criterion for our study. As such, it is possible that we excluded patients who did not have a blood type listed in their medical chart; therefore, findings pertaining to our secondary objectives may not include all eligible patients. Also, patients who have a blood type on file may have more comorbidities than those without a recorded blood type.

Data from one institution makes it challenging to draw conclusions that pertain to the entire population affected by COVID-19. Our institution does have a unique advantage of serving a population that is generally underrepresented in the literature. Lastly, there is a possibility that the discrepancy found between clinical outcomes between genders may be secondary to confounding factors not addressed in this study.

Conclusions

In a large cohort of COVID-19 patients treated at a university based, tertiary care safety net hospital in New Orleans, LA, blood type was not a significant predictor of clinical course or death. Older age, male gender, and comorbidities were significant prognosticators of death, while older age and male gender were the only significant factors associated with a worse clinical course. Race was not a significant predictor of death in our population and was associated with an increased, but not significantly increased morbidity score. Larger studies likely would show race as significant in predicting clinical course.

This is the first study that employed a morbidity scoring system to quantify the clinical course among patients with COVID-19.

Contributions

K.E.T., A.K., E.D., A.G.C., M.M.L. conceived and designed the analysis; K.E.T., A.K., E.D. collected the data; K.E.T., A.K., E.D., A.G.C., M.M.L. contributed data or analysis tools; A.G.C. performed the analysis; K.E.T., A.K., E.D., A.G.C., M.M.L. wrote the paper.

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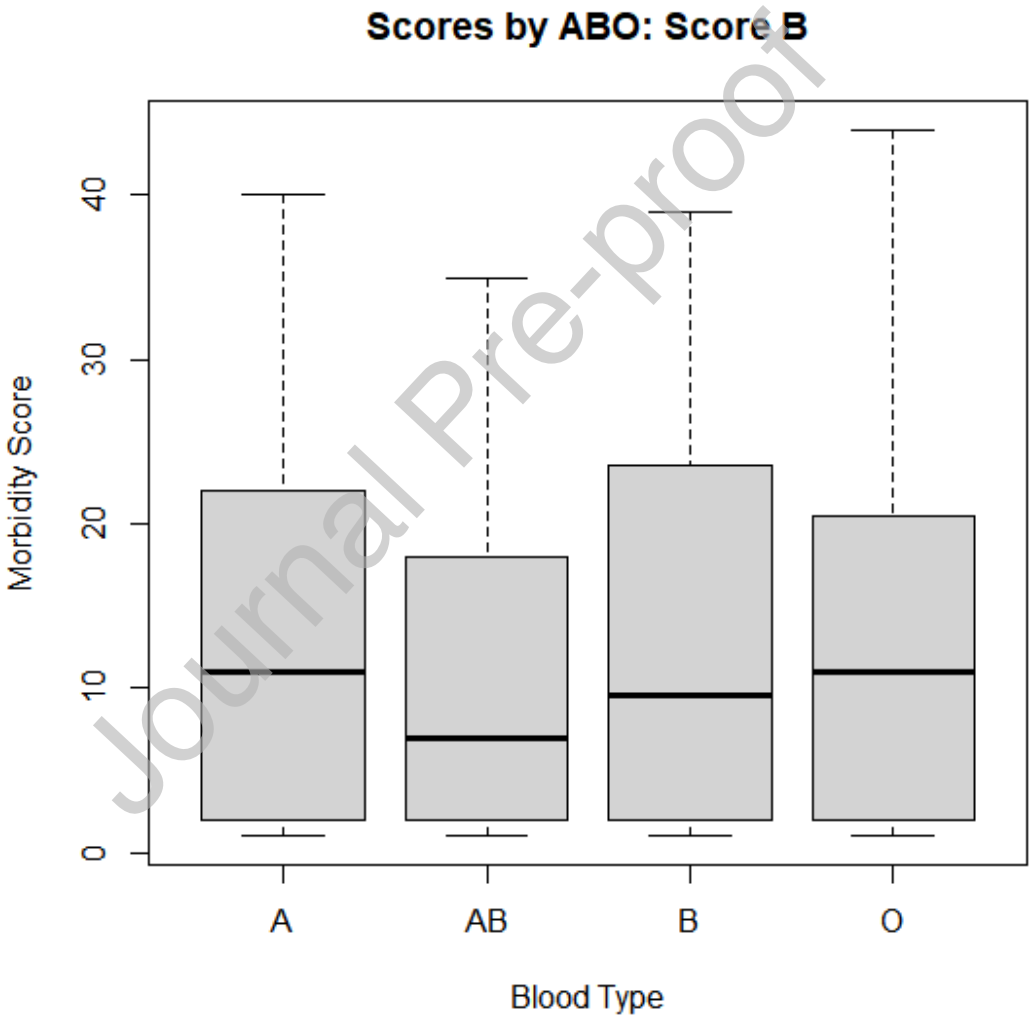

Figure 1: Box plot of COVID-19 morbidity scores for each blood type group.
ABO: blood type group

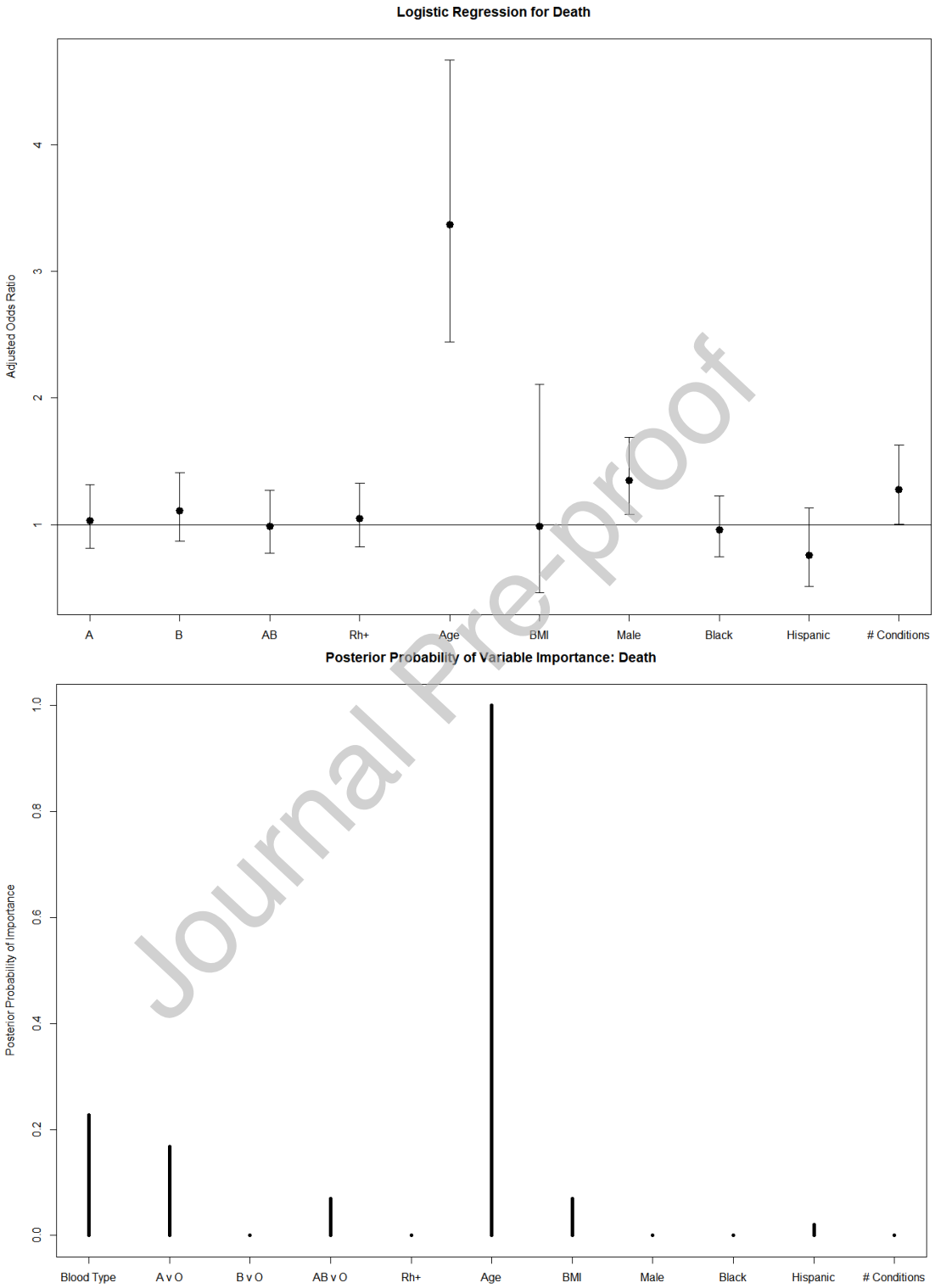

Figure 2: Logistic regression for death and Bayesian variable selection for logistic regression for death.

Variable	O (328)	A (180)	B (128)	AB (33)	P-value
Rh+	305 (93)	166 (92.2)	116 (90.6)	33 (100)	0.313
Male	110 (33.5)	83 (46.1)	47 (36.7)	7 (21.2)	0.009
Black Race	220 (67.1)	118 (65.6)	108 (84.4)	26 (78.8)	0
Hispanic Ethnicity	46 (14)	23 (12.8)	9 (7)	1 (3)	0.073
Heart Disease	51 (15.5)	28 (15.6)	24 (18.8)	3 (9.1)	0.616
Lung Disease	53 (16.2)	25 (13.9)	21 (16.4)	5 (15.2)	0.902
Hypertension	197 (60.1)	116 (64.4)	83 (64.8)	15 (45.5)	0.168
Diabetes Mellitus	102 (31.1)	62 (34.4)	42 (32.8)	4 (12.1)	0.069
Kidney Disease	37 (11.3)	24 (13.3)	20 (15.6)	1 (3)	0.211
Blood Clot	9 (2.7)	12 (6.7)	9 (7)	2 (6.1)	0.073
Vascular Disease	34 (10.4)	24 (13.3)	20 (15.6)	3 (9.1)	0.411
Cancer	37 (11.3)	29 (16.1)	13 (10.2)	5 (15.2)	0.317
Tobacco Use	4 (1.2)	2 (1.1)	3 (2.3)	0 (0)	0.788
Sleep Apnea	2 (0.6)	0 (0)	1 (0.8)	0 (0)	0.654
Hyperlipidemia	2 (0.6)	2 (1.1)	1 (0.8)	0 (0)	0.878
Metabolic Disorder	93 (28.4)	54 (30)	33 (25.8)	6 (18.2)	0.544
Alcohol Abuse	4 (1.2)	3 (1.7)	4 (3.1)	1 (3)	0.372
Liver Disease	3 (0.9)	1 (0.6)	2 (1.6)	1 (3)	0.374
HIV	9 (2.7)	0 (0)	4 (3.1)	0 (0)	0.066
Sickle Cell Disease	4 (1.2)	1 (0.6)	1 (0.8)	0 (0)	0.901
Substance Use Disorder	3 (0.9)	3 (1.7)	0 (0)	0 (0)	0.567
Stroke	35 (10.7)	24 (13.3)	18 (14.1)	3 (9.1)	0.652
# Comorbidities	2.33 (2.15)	2.54 (2.23)	2.58 (2.2)	1.64 (1.88)	0.087
Age	53.28 (20.12)	55.28 (18.19)	52.99 (18.32)	53.03 (21.74)	0.652
BMI	30.55 (9.11)	31.02 (8.29)	31.9 (8.37)	228.36 (1137.82)	0.334

Table 1: Demographic differences between blood typing groups.
BMI: body mass index; HIV: human immunodeficiency virus; Rh+: Rhesus blood group system; #: number

Criteria	Score
Outpatient Diagnosis	1
ED admission	2
Admitted	3
ICU	5
MI	4
VTE	4
STROKE	5
SUPPLEMENTAL O2	3
INTUBATION	5
AKI NO HD	2
AKI HD	5
STEROIDS	2
REMDESIVIR	2
HYDROXYCHLOROQUINE	2
AZITHROMYCIN	2
Length Hospitalization 0-1d	1
Length Hospitalization 2-5d	2
Length Hospitalization 6-10d	3
Length Hospitalization 11-20d	4
Length Hospitalization >20d	5
Death	50

Table 2: Scoring systems used to obtain total morbidity score.
AKI: Acute kidney injury; d: day; ED: emergency department; HD: hemodialysis; ICU: intensive care unit; MI: myocardial infarction; O2: oxygen; VTE: venous thromboembolism.

Outcome Variable	O (328)	A (180)	B (128)	AB (33)	P-value
Expired	51 (15.5)	33 (18.3)	23 (18)	5 (15.2)	0.829
Morbidity Score Components					
Admitted	208 (63.4)	120 (66.7)	73 (57)	18 (54.5)	0.261
ICU	101 (30.8)	59 (32.8)	42 (32.8)	8 (24.2)	0.793
ED admission	203 (61.9)	116 (64.4)	76 (59.4)	17 (51.5)	0.505
Outpatient Diagnosis	126 (38.4)	62 (34.4)	53 (41.4)	13 (39.4)	0.649
MI	18 (5.5)	10 (5.6)	3 (2.3)	2 (6.1)	0.453
VTE	12 (3.7)	8 (4.4)	5 (3.9)	1 (3)	0.961
STROKE	8 (2.4)	5 (2.8)	5 (3.9)	0 (0)	0.732
SUPPLEMENTAL.O2	149 (45.4)	86 (47.8)	51 (39.8)	14 (42.4)	0.568
INTUBATION	70 (21.3)	41 (22.8)	31 (24.2)	7 (21.2)	0.916
AKI.NO.HD	59 (18)	30 (16.7)	21 (16.4)	2 (6.1)	0.39
AKI.HD	30 (9.1)	18 (10)	16 (12.5)	2 (6.1)	0.673
Received Treatment for					
Steroids	43 (13.1)	27 (15)	18 (14.1)	3 (9.1)	0.854
Remdesevir	12 (3.7)	0 (0)	3 (2.3)	0 (0)	0.03
Hydroxychloroquine	103 (31.4)	60 (33.3)	45 (35.2)	11 (33.3)	0.877
Azithromycin	111 (33.8)	49 (27.2)	48 (37.5)	12 (36.4)	0.232
Morbidity Score	12.98 (10.75)	13.31 (10.94)	13.03 (11.66)	11.39 (10.95)	0.656

Table 3: COVID-19 outcomes by blood type group.
AKI: Acute kidney injury; ED: emergency department; HD: hemodialysis; ICU: intensive care unit; MI: myocardial infarction; O2: oxygen; VTE: venous thromboembolism.

Variable	aME (CI)	P-value
A v O	0.98 (0.92-1.039)	.462
B v O	0.99 (0.932-1.054)	.784
AB v O	0.98 (0.918-1.041)	.485
Rh+	0.98 (0.929-1.042)	.578
Age	1.45 (1.349-1.555)	<.001
BMI	0.95 (0.811-1.113)	.528
Male	1.17 (1.109-1.243)	<.001
Black	1.07 (0.998-1.141)	.059
Hispanic	0.99 (0.916-1.067)	.772
# Conditions	1.02 (0.954-1.088)	.573

Table 4: Quasi-Poisson regression results – adjusted multiplicative effects and associated 95% confidence interval.
BMI: body mass index; Rh+: rhesus blood group system; v: versus; #: number